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Physicochemical aspects of drug release. XVI. The effect of storage on drug dissolution from solid dispersions and the influence of cooling rate and incorporation of surfactant

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Summary

Solid dispersions of 10% w/w griseofulvin were prepared with polyethylene glycol (PEG) 3000 or xylitol as carriers, with or without the incorporation of 2% w/w sodium dodecyl sulphate (SDS). The dispersions were cooled either slowly at room temperature or rapidly in liquid nitrogen. The dispersions were stored under controlled conditions at 25, 35 and 45°C and dissolution rate studies, particle size measurements, phase analysis and heat of fusion measurements were performed at intervals during 10 months. In dispersions with PEG as carrier, without SDS, griseofulvin was present in crystalline form. The dissolution rate was unchanged during storage for dispersions prepared with slow cooling, but decreased for dispersions prepared with rapid cooling. This may have been caused by an increase in PEG crystallinity with storage time. With the incorporation of SDS, the dissolution rate initially increased considerably for dispersions with PEG as carrier. Griseofulvin was dissolved in the carrier/surfactant system in dispersions prepared with slow cooling, whereas griseofulvin was present in pure crystalline form in corresponding dispersions prepared with rapid cooling. Dispersions stored at 45°C liquified on storage independent of cooling procedure and were excluded from the study. The dissolution rate decreased considerably for dispersions prepared with slow cooling, since the dissolution of PEG was impaired by the incorporation of SDS. The dissolution rate of dispersions prepared with rapid cooling also decreased with storage temperature. Griseofulvin was present in crystalline form in all dispersions with xylitol as carrier and the dissolution rate and particle size remained unchanged irrespective of storage temperature and time. The dissolution rate was increased with the incorporation of SDS, but not to the same extent as in PEG dispersions. With increase in storage temperature the dissolution rate decreased, because of decreased dissolution of xylitol with the incorporation of SDS.

Introduction

Solid dispersions can be used to increase the dissolution rate of drugs with low aqueous solubility. Generally, the dissolution rate of drugs in

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particulate form in solid dispersions is increased with decrease in drug particle size. The growth of the particle can be controlled by varying the conditions during melting and crystallization. Rapid cooling of a hot saturated solution yields small crystals, whereas a low crystallization rate can produce large particles (Hüttenrauch, 1983). Rapid cooling of solid dispersions can result in increased dissolution rates compared to those obtained with slowly cooled dispersions (e.g., Collett et al., 1976; Kassem et al., 1979; McGinity et al., 1984), and this effect has been explained by the smaller drug particle size. Kaur et al. (1980) found relatively small differences and no obvious relationship between size distribution and cooling rates for dispersions of tolbutamide in PEG 2000. Thus it seems that not only the drug particle size but also the possible formation of amorphous or metastable states of the drug (McGinity et al., 1984) and the polymer obtained by rapid cooling, which will influence the dissolution (Chatham, 1987), are of importance.

Despite the vast amount of research made in the field of solid dispersions with different carriers and drugs, there are few products on the market using the concept of solid dispersions. One of the reasons is related to stability problems (e.g., Kreuter, 1983; Bloch and Speiser, 1987). The dissolution behaviour of solid dispersions can be changed on storage, due to changes in physico-chemical characteristics of the drug, the carrier or both (Craig, 1989). Drugs in molecular form may precipitate due to supersaturation and dispersed-phase particles can coarsen on storage (Chiou and Riegelman, 1971). Drugs dispersed in crystalline form can be expected to be less reactive than the amorphous or metastable polymorphic forms (Chatham, 1987). The dissolution rate of the polymer carrier itself may decrease on storage, since for example, an amorphous polymer may recrystallize to give a polymer of a higher degree of crystallinity (Chatham, 1987). The incorporated drug may also induce changes in crystallinity of the carrier (Ford et al., 1986).

In dispersions using PEG as carrier both unchanged and decreased dissolution rates have been reported after storage, whereas increased dissolution rates after longer storage times have not been obtained. Unchanged dissolution rates after one year of storage at ambient temperature have been reported for drugs dispersed in PEG of different molecular weight (Chiou, 1977; Ravis and Chen, 1981; Alonso et al., 1988; Sjökvist et al., 1992).

Hoelgaard and Møller (1975) reported a decrease in dissolution rate for testosterone in various PEGs, which was ascribed to particle coarsening. Ford and Rubinstein (1979) found that ageing markedly reduced the dissolution rate of indomethacin in PEG 6000 and that the change was dependent on drug concentration and storage conditions. The dependence of concentration on the effects of ageing was suggested to imply that the diffusion of drug through the solid dispersion matrix played an important role in ageing. Different patterns in the dissolution rates of eight drugs dispersed in PEG 6000 after storage at different temperatures for 12 weeks were reported by Dubois et al. (1985). It thus seems that the changes on storage are dependent on each specific drug/carrier combination.

In previous studies (Sjökvist et al., 1991, 1992) the surfactant sodium dodecyl sulphate, SDS, was incorporated in dispersions of griseofulvin in PEG 3000 and was shown to increase the dissolution rate considerably. Using X-ray powder diffraction it was shown that the increase in dissolution rate was due to the formation of a solid solution. A decrease in dissolution rate was observed after storage for one year at ambient temperature (Sjökvist et al., 1992). Xylitol has been reported to have good dissolution properties in solid dispersions (Sjökvist and Nyström, 1991). Bloch et al. (1982) found, however, that the dissolution rate of hydrochlorothiazide dispersed in xylitol decreased on storage for two months, due to crystallization of the drug.

Thus, several studies have reported that a decrease in dissolution rate after storage could be due to crystallization of the drug, drug particulate coarsening or structural changes in the carrier. However, the importance of formulation and processing factors on the stability of the dissolution rate of solid dispersions is still not widely understood. In this context, it has not been evaluated in any detail whether the use of drugs in molecular form represents any advantage or disadvantage in comparison to dispersions containing the drug in particulate form.

In this study solid dispersions of 10% w/w griseofulvin were prepared by the melting method with PEG 3000 and xylitol as carriers. The dispersions, with or without 2% w/w SDS incorporated, were cooled either slowly at room temperature or rapidly in liquid nitrogen and stored under controlled conditions. The systems used represent dispersions in which the drug is in both molecular and particulate form. The aim of the study was to investigate the influence of cooling rate and surfactant incorporation on drug dissolution rate, particle size and physical state after storage.

Experimental

Materials

Griseofulvin, microsized (Glaxo, U.K.), was used as a model substance for a practically insoluble drug. This quality has been used in earlier studies (Sjökvist and Nyström, 1988, 1991; Sjökvist et al., 1991, 1992).

Polyethylene glycol (PEG) 3000 (Apoteksbolaget, Sweden) and xylitol (Finnish Sugar, Finland) were used as water soluble carriers. These carriers have been used in earlier studies (Sjökvist and Nyström, 1988, 1991; respectively).

Sodium dodecyl sulphate (SDS) (Apoteksbolaget, Sweden) is an anionic surfactant. It has earlier been used in solid dispersions (Sjökvist et al., 1991, 1992).

Methods

Preparation of solid dispersions

100 g batches of dispersions of 10% w/w griseofulvin in the two carriers were prepared with and without the incorporation of 2% w/w SDS.

PEG as carrier Dispersions were prepared as described earlier (Sjökvist et al., 1992). When a clear melt was obtained, the melt was cooled either slowly at ambient temperature or rapidly by pouring the melt into liquid nitrogen. The obtained solids were stored overnight at ambient temperature and pulverized and sieved to obtain the fraction 300–500 μm. As references, samples of recrystallized PEG, with and without SDS incorporated, were prepared in the same manner.

Xylitol as carrier Dispersions were prepared on a hotplate at 160°C. After approx. 1 h the white viscous melt was cooled either slowly or rapidly. Slowly cooled dispersions were transferred to a warming cupboard thermostated to 45°C and left over night, in order to improve the speed of crystallization, which otherwise is slow (Sjökvist and Nyström, 1991). Dispersions cooled rapidly in liquid nitrogen were also kept overnight in the thermostated cupboard. The resulting brittle solids were pulverized to obtain the fraction 300–500 μm. As references, samples of recrystallized xylitol, with and without SDS incorporated, were prepared in the same manner.

Storage conditions

A full characterization of the dispersions was carried out after 0, 1, 2 and 4 months. Additional measurements were made after 8 months (X-ray analysis), 9 months (dissolution rate studies) and 10 months (thermal analysis and particle size measurements). After preparation, samples were kept in desiccators in warming cupboards thermostated to 25, 35 or 45°C. In order to maintain the relative humidity fairly constant (approx. 32%) the samples were kept over saturated solutions of $MgCl_2$ (Nyqvist, 1983). The relative humidity may have been altered for the samples stored at 45°C for a minor period between the measurements at 4 and 10 months.

The dispersions incorporating SDS in PEG prepared by slow cooling and stored at 45°C became sticky and progressively liquid on storage. The same dispersion prepared with rapid cooling and stored at 45°C also became sticky upon storage, but not to the same extent. However, after 8 months this dispersion was also in liquid form. These dispersions were consequently excluded from the study.

Characterisation of solid dispersion properties

Drug dissolution rate Dissolution rate tests were performed as described earlier (Sjökvist et al., 1992) according to USP XXI (paddle method, 100 rpm) in a dissolution medium of 0.9% sodium chloride and 0.01% polysorbate 80. The results presented are mean values of at least three determinations. The initial dissolution rate was calculated from the initial slope of the dissolution profiles.

Carrier dissolution rate The USP XXI disintegration test, basket rack assembly without discs, was used as a simplified carrier dissolution rate test, as described earlier (Sjökvist et al., 1989). Compacts of slowly cooled freshly prepared dispersions of xylitol and dispersions of xylitol stored at 25 and 45°C for 17 months were prepared and tested for carrier dissolution time in 900 ml 0.9% sodium chloride and 0.01% polysorbate 80 at 21°C. The presented results are mean values of six compacts.

Particle size analysis Size measurements of griseofulvin particles in the solid dispersions were made with a Coulter Counter TA II, as described earlier (Sjökvist and Nyström, 1988). In this study particles larger than 0.6 μm were characterized using the 30 μm aperture tube. Tests were made to ensure that PEG 3000 or xylitol did not affect the results. The results presented are mean values of at least two determinations.

X-ray diffraction Phase analysis was carried out using X-ray powder diffraction as described earlier (Sjökvist et al., 1992) on a single sample of each dispersion. Samples were transferred to a container and kept at ambient temperature overnight before measurements were made.

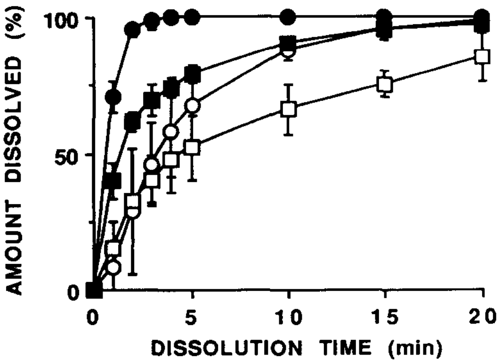

Fig. 1. Dissolution rate profiles for solid dispersions of 10% w/w griseofulvin with PEG as carrier. (○, ●) slow cooling; (□, ■) rapid cooling. Open symbols: no SDS incorporated; Closed symbols: 2% w/w SDS incorporated. Error bars represent the 95% confidence intervals for the mean.

Thermal analysis Heat of fusion measurements were carried out as described earlier (Sjökvist et al., 1992). For samples containing PEG, integrations were made in the temperature range 30–200°C. For samples with xylitol as carrier, integrations were made in the temperature ranges 70–200 and 200–220°C. The same calibration baseline was used for measurements at 0, 1, 2 and 4 months, while a new calibration baseline was used for the last measurements after 10 months of storage. The results presented are mean values of at least two determinations.

Results and Discussion

Characterization of dispersions with PEG as carrier

The influence of cooling rate and incorporation of SDS on freshly prepared dispersions

The dissolution rate profiles for dispersions of 10% w/w griseofulvin with PEG as carrier are presented in Fig 1. The dissolution was considerably enhanced by the incorporation of SDS, which is in agreement with earlier studies (Sjökvist et al., 1991, 1992). For dispersions prepared with rapid cooling the dissolution rates were initially similar to those of dispersions prepared with slow cooling, but a decrease in dissolution rate was then observed.

The relative amount of each phase in the solid dispersion can be determined by X-ray powder diffraction (Cullity, 1978; Sjökvist et al., 1991, 1992). The results from the X-ray powder diffraction analysis are presented in Table 1. Griseofulvin was present in pure crystalline form in dispersions without SDS. The ratio between phases was somewhat lower for the dispersion prepared with rapid cooling. From the X-ray diffractogram it was observed that the PEG diffraction pattern was more diffuse over the 2θ range observed. At the position for the chosen griseofulvin line the background intensity was more pronounced than for the correponding dispersion that had been cooled slowly. This results in a lower intensity

TABLE 1

X-ray powder diffraction analysis of solid dispersions of 10% w/w griseofulvin in PEG 3000 stored at 25°C

Sample (−)	Ratio [a]				
	Storage time (months)				
	0	1	2	4	8
Without SDS					
Slowly cooled	0.8 [b]	0.8	0.6	0.8	0.8
Rapidly cooled	0.5	1	0.9	0.8	1
With 2% w/w SDS incorporated					
Slowly cooled	0 [b]	0	0 [c]	0 [c]	0 [c]
Rapidly cooled	0.9	0.9	0.9	1	1

[a] The ratio of the intensity of a characteristic line of the griseofulvin phase to that of the PEG-containing phase.

[b] From Sjökvist et al. (1992).

[c] The size of the particles is in the range where intensity measurements by X-ray diffraction are uncertain.

TABLE 2

Particle size characteristics of griseofulvin in solid dispersions with PEG 3000 prepared with slow cooling and stored at 25°C [a]

Sample (−)	Geometric mean diameter [b] d_{v_g} (μm)	Number of particles in 1 ml suspension [c]	Amount recovered [d] (%)
10% w/w griseofulvin			
0 month	2.3 (1.8)	40200	67
2 months	2.2 (2.0)	38800	49
10 months	1.6 (1.8)	46000	72
10% w/w griseofulvin + 2% w/w SDS			
0 month	4.9 (1.8)	3300	18
2 months	10.3 (1.4)	4000	95
10 months	9.6 (1.6)	4700	88

[a] Weight frequency distributions obtained by Coulter Counter TA II.

[b] Log-normal distributions characterized by geometric mean and geometric standard deviations (dimensionless) given in parentheses.

[c] Due to the lower detection level of the Coulter this figure represents particles > 0.6 μm.

[d] Calculated weight of griseofulvin particles monitored during Coulter measurement, in relation to nominal amount.

ratio for the griseofulvin and PEG lines used here, although the relative amount of griseofulvin might be unchanged.

In dispersions incorporating SDS prepared with slow cooling griseofulvin was present in solid solution in the PEG/SDS system. However, in the corresponding dispersion prepared with rapid cooling griseofulvin was present in crystalline form. This may be because the temperature interval, at which it is energetically favourable for the monomers of SDS to form aggregates, was passed too quickly by the cooling procedure. As these aggregates are crucial for the bonding of griseofulvin in molecular form (Aldén et al., 1992) no solid solution was formed.

The particle size characteristics for griseofulvin in dispersions of PEG are presented in Table 2. For dispersions prepared with rapid cooling it was not possible to dissolve the carrier rapidly enough to obtain a stock suspension of griseofulvin, and large flakes of the dispersion were present in the stock suspension. Consequently, the particle size could not be measured in rapidly cooled PEG dispersions.

The stock suspension for the dispersion without SDS was cloudy and the total amount of particles in 1 ml was approx. 40000, with a particle size of 2.3 μm, which is in agreement with earlier results (Sjökvist and Nyström, 1988). This supports the findings from the phase analysis that griseofulvin is in particulate form in this dispersion. The stock suspensions of the dispersion incorporating SDS were only slightly cloudy and the total amount of particles in 1 ml was approx. 3300, with a mean particle size of 4.9 μm. The amount of particles recovered was only 18%,

TABLE 3

Heat of fusion of freshly prepared solid dispersions with 10% w/w griseofulvin

Sample (−)	Heat of fusion (J g^{-1}) [a]	
	Carrier	
	PEG 3000	Xylitol
Without SDS		
Slowly cooled	164 ± 1	224 ± 0
Rapidly cooled	165 ± 6	234 ± 1
With 2% w/w SDS incorporated		
Slowly cooled	153 ± 1	216 ± 3
Rapidly cooled	157 ± 0	215 ± 7

[a] Mean ± SD.

supporting the result that the vast majority of griseofulvin was in molecular form, or smaller than the lower detection limit of 0.6 μm.

The results from heat of fusion measurements are presented in Table 3. The heat of fusion values for dispersions without SDS were similar for dispersions prepared with the two cooling procedures. However, the heat of fusion values were lower for the corresponding dispersions incorporating SDS, which is in agreement with earlier reports (Sjökvist et al., 1991, 1992).

It can be concluded that the initial dissolution rates were similar for dispersions prepared with the two cooling procedures, but after the initial period the dissolution rate decreased for dispersions cooled rapidly. With the incorporation of SDS the dissolution increased considerably. Using X-ray diffraction it was observed that griseofulvin was present in pure crystalline form in dispersions without SDS irrespective of cooling procedure, and in the rapidly cooled dispersion incorporating SDS, whereas griseofulvin was in solid solution in the dispersion incorporating SDS which had been cooled slowly. The difference in dissolution obtained for dispersions incorporating SDS cooled differently, was probably caused by the fact that griseofulvin was present in crystalline form in the dispersion cooled rapidly, and was in solid solution in the dispersion cooled slowly.

The influence of storage on dispersions without SDS prepared with different cooling rates

For dispersions prepared with slow cooling and stored at 25 and 35°C, the dissolution rate was fairly constant (Fig. 2a), indicating that the dispersion was stable under these storage conditions. The particle size of griseofulvin in disper-

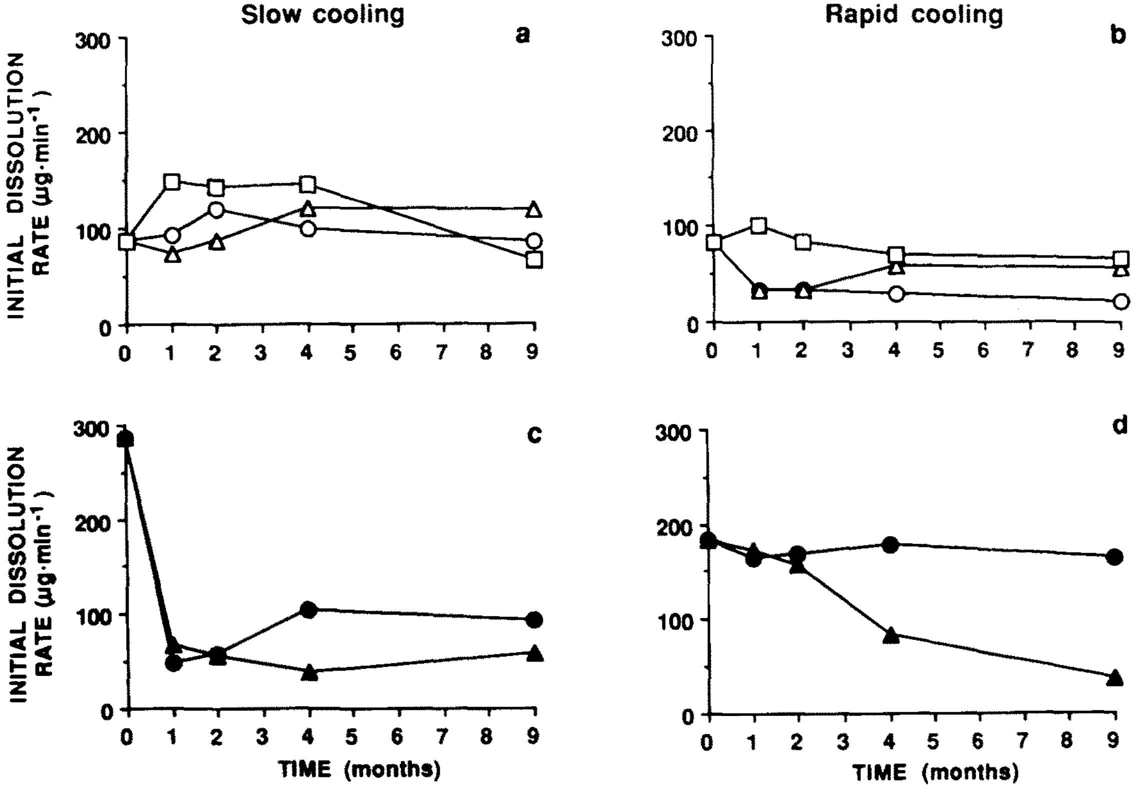

Fig. 2. Initial dissolution rate for solid dispersions of 10% w/w griseofulvin with PEG as carrier vs storage time: Storage temperature: (○, ●) 25°C; (△, ▲) 35°C; (□) 45°C. Open symbols: no SDS incorporated; Closed symbols: 2% w/w SDS incorporated.

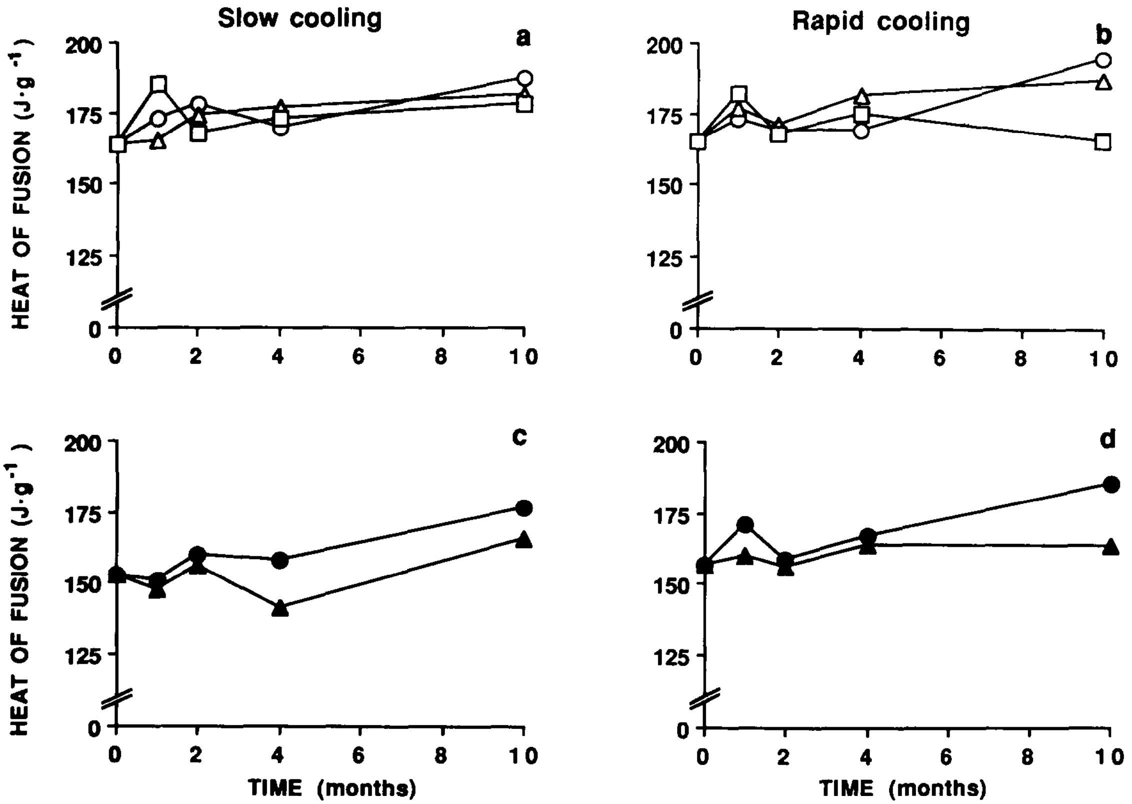

Fig. 3. Heat of fusion of solid dispersions of 10% w/w griseofulvin with PEG as carrier. Symbols as in Fig. 2.

sions stored at 25°C was constant at approx. 2 μm (Table 2) and the ratio between phases for this dispersion did not change during the storage period (Table 1). The dispersion stored at 45°C showed an increase in dissolution during the first four months which was decreased to more or less the initial dissolution rate after 9 months of storage. For slowly cooled dispersions (Fig. 3a) the heat of fusion was constant for the dispersions stored at all three temperatures.

For dispersions cooled rapidly the dissolution of the dispersion stored at 45°C was more or less unchanged (Fig. 2b). However, for dispersions stored at 25 and 35°C the dissolution rates were halved after 1 month of storage (Fig. 2b). The dissolution rate remained at this level for dispersion stored at 25°C, whereas an increase was obtained for the dispersion stored at 35°C after 4 months. The results from the dissolution rate studies are in agreement with the results from the heat of fusion measurements. The heat of fusion value for the dispersion stored at 45°C was more or less unchanged, but was increased for the dispersions stored at the two other temperatures and especially for the dispersion stored at 25°C, which may have been due to increased crystallinity.

From the results it was concluded that dispersions prepared with slow cooling were fairly stable systems and that the solid states of griseofulvin and PEG were more or less unchanged, resulting in unchanged dissolution rates. This may be because the drug in the freshly prepared dispersion was already in particulate form, as observed by Dordunoo et al. (1991). Furthermore, the dissolution of PEG itself seemed to be unchanged. For dispersions prepared with rapid cooling and stored at 25°C the X-ray diffractogram indicated a change towards increased order in the PEG structure and the heat of fusion values were increased. The dissolution rate of rapidly cooled PEG could thus be decreased on storage.

The influence of storage on dispersions incorporating SDS

With the incorporation of 2% w/w SDS the dissolution rate was initially considerably increased (Fig. 2c), but decreased after 1 month (Fig. 2c) and became even slower than the dissolution of the dispersion without SDS. The amount of particles recovered increased from 20 to 90% and the particle size was increased from approx. 5 μm to 10 μm. From the X-ray analysis it was observed that griseofulvin was not in pure crystalline form (Table 1). However, the size of the particles was in the range where intensity measurements by X-ray diffraction are uncertain. A certain amount of griseofulvin in particulate form may also be present without being detected by X-ray diffraction, where the detection limit is at approx. 2% (Sjökvist et al., 1991). Further investigation is needed before conclusions can be drawn. Another possible contribution to the decrease in drug dissolution can be that dissolution of PEG itself was impaired during storage by the incorporation of SDS (Sjökvist et al., 1992). The decrease in dissolution rate is thus not a consequence solely of drug particle coarsening.

For the dispersion cooled rapidly and stored at 25°C the dissolution rate was fairly constant during the storage period (Fig. 2d), whereas a considerable decrease in dissolution rate was obtained for the dispersion stored at 35°C. Griseofulvin was present in crystalline form in the dispersion stored at 25°C during the storage period (Table 1). Due to the incorporation of SDS these dispersions were easily wetted, and thus the dissolution rate was faster than for dispersions without SDS. The heat of fusion values were initially lower than those for corresponding dispersions without SDS (Fig. 3c and d) and were quite constant during the first 4 months (Fig. 3c and d). However, after 10 months the value increased.

The dissolution rate increased with the incorporation of SDS, but a pronounced sensitivity was induced in the dispersion and the dissolution decreased on storage. On the incorporation of SDS, a solid solution of griseofulvin was initially formed in the dispersion prepared with slow cooling, but particles precipitated on storage and in combination with a decrease in dissolution of PEG by the incorporation of SDS, the dissolution rate of griseofulvin decreased. In the dispersions prepared with rapid cooling griseofulvin was present in crystalline form. The dissolution rate was unchanged on storage for the dispersion stored at 25°C, but decreased with increase in storage temperature.

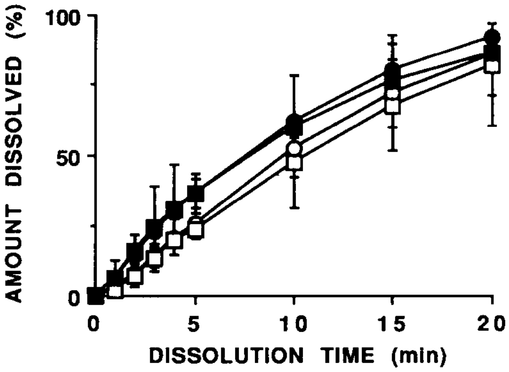

Fig. 4. Dissolution rate profiles for solid dispersions of 10% w/w griseofulvin with xylitol as carrier: (○, ●) slow cooling; (□, ■) rapid cooling. Open symbols: no SDS incorporated; Closed symbols: 2% w/w SDS incorporated. Error bars represent the 95% confidence intervals for the mean.

Characterization of dispersions with xylitol as carrier

The influence of cooling rate and incorporation of SDS on freshly prepared dispersions

The dissolution profiles for dispersions with xylitol as carrier are presented in Fig. 4. It can be observed that the dissolution rate was much faster for dispersions with PEG as carrier (Fig. 1) than for those using xylitol. The cooling rate did not influence the dissolution rate, but the incorporation of SDS did increase the extent of dissolution slightly.

In all dispersions with xylitol as carrier, the pure griseofulvin and carrier phases were identified and griseofulvin was present in crystalline form. The ratio between phases was the same,

TABLE 4

X-ray powder diffraction analysis of solid dispersions of 10% w/w griseofulvin in xylitol stored at 25°C

Sample (−)	Ratio [a]				
	Storage time (months)				
	0	1	2	4	8
Without SDS					
Slowly cooled	0.2	0.2	0.2	0.2	0.2
Rapidly cooled	0.2	0.2	0.3	0.2	0.2
With 2% w/w SDS incorporated					
Slowly cooled	0.2	0.2	0.2	0.2	0.2
Rapidly cooled	0.2	0.2	0.2	0.2	0.3

[a] The ratio of the intensity of a characteristic line of the griseofulvin phase to that of the xylitol phase.

irrespective of cooling procedure and incorporation of SDS (Table 4).

The particle size characteristics for griseofulvin dispersed in xylitol are presented in Table 5. In contrast to dispersions with PEG as carrier, there were no problems associated with the measurement of griseofulvin in dispersions with xylitol as carrier, regardless of dispersion system. The amount recovered, i.e., the calculated weight of griseofulvin particles monitored during the Coulter measurements in relation to the nominal amount, was approx. 100% in all measurements for dispersions with xylitol as carrier. The particle size was more or less uninfluenced by the incorporation of SDS and the cooling rate.

In the DSC scans of dispersions with xylitol as carrier there were two peaks (Fig. 5). The first peak, at approx. 93–94°C, represents the melting of the mixture of xylitol and griseofulvin and the second peak, at approx. 212°C, corresponds to the melting of the remaining particles of griseofulvin. The reason that this peak was present in the DSC scans of dispersions with xylitol as carrier but not in dispersions with PEG as carrier may lie in differences in the procedure of preparation. In dispersions with PEG as carrier, griseofulvin was dissolved in the melted carrier prior to the cooling process, whereas in dispersions with xylitol as carrier a suspension of griseofulvin was obtained and then cooled. The solubility of griseofulvin thus seems to be higher in PEG than in xylitol at the elevated temperature. During the cooling procedure of the xylitol dispersions, the griseofulvin particles may have coarsened and become larger than the raw material of griseofulvin.

The heat of fusion values for dispersions with xylitol as carrier are presented in Table 3. The value was somewhat higher in the dispersion prepared with rapid cooling. In dispersions incorporating SDS the heat of fusion values were similar irrespective of cooling rate. The second peak in the DSC scans of dispersions incorporating 2% w/w SDS was smaller and more flat and started at a lower temperature compared to dispersions without SDS.

TABLE 5

Particle size characteristics of griseofulvin in solid dispersions in xylitol [a]

Sample	Geometric mean diameter [b] d_{v_g} (μm)					
	Storage time (months)					
	0	2		10		
		25°C	45°C	25°C	35°C	45°C
10% w/w griseofulvin						
Slowly cooled	4.5 (1.7)	4.3 (1.6)	4.1 (1.6)	3.7 (1.6)	3.3 (1.6)	4.4 (1.6)
Rapidly cooled	4.4 (1.7)	4.5 (1.7)	– [c]	4.6 (1.8)	3.6 (1.7)	4.1 (1.7)
10% w/w griseofulvin + 2% w/w SDS						
Slowly cooled	4.7 (1.6)	5.4 (1.7)	5.4 (1.6)	3.7 (1.6)	3.4 (1.6)	5.7 (1.7)
Rapidly cooled	3.8 (1.7)	3.8 (1.7)	4.7 (1.8)	3.9 (1.7)	3.1 (1.7)	5.5 (1.7)

[a] Weight frequency distributions obtained by Coulter Counter TA II.

[b] Log-normal distributions characterized by geometric mean and geometric standard deviations (dimensionless) given in brackets.

[c] Not measured.

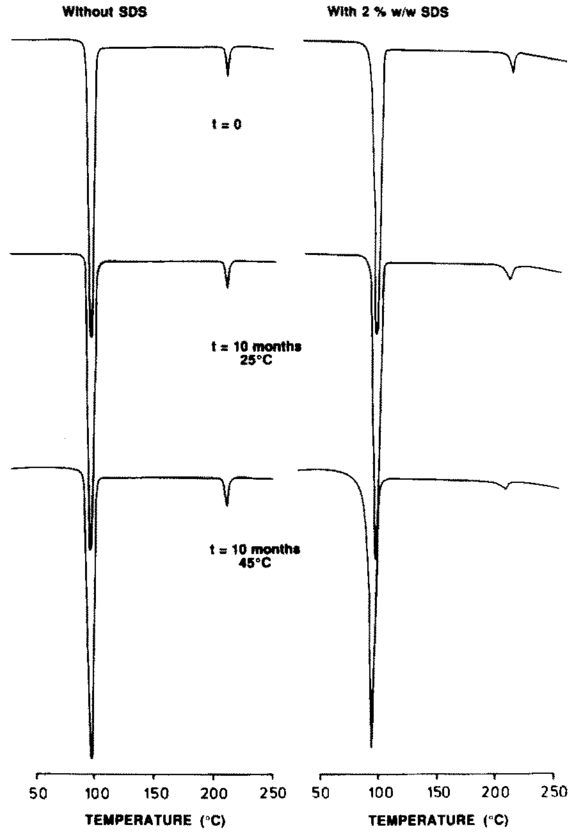

Fig. 5. DSC scans of dispersions of 10% w/w griseofulvin with xylitol as carrier with or without SDS incorporated at time 0 and after 10 months of storage at 25°C and 45°C.

It can be concluded that griseofulvin was present in crystalline form in all dispersions with xylitol. The cooling procedure and the incorporation of SDS did not have any pronounced effect on the dissolution and incorporated state of griseofulvin.

The influence of storage on dispersions without SDS prepared with different cooling rates

The dissolution rate was more or less unaffected by storage, irrespective of storage temperature, for dispersions prepared with the two cooling procedures (Fig. 6a and b). These results are in agreement with those from the particle size measurements (Table 5). The particle size did not change to any large extent for the dispersions, irrespective of storage temperature and time. The ratio between phases was also fairly constant during storage for all these dispersions (Table 4). The heat of fusion values were quite constant during the first 4 months, after which a slight increase was observed (Fig. 7a and b). For these dispersions the heat of fusion for the second peak in the DSC scan was between 10 and 11 J/g.

It can thus be concluded that solid dispersions with xylitol as carrier were stable under these storage conditions, irrespective of cooling rate. There was no change in phase composition and the particle size was fairly constant regardless of cooling rate and storage temperature, which led to an unchanged dissolution rate.

The influence of storage on dispersions incorporating SDS

The incorporation of SDS increased the dissolution rate for griseofulvin dispersed in xylitol (Fig. 6c and d), but not to the same extent as in dispersions of PEG (Fig. 2c and d). The general tendency for dispersions incorporating SDS was that dispersions stored at 25°C showed a minor decrease (Fig. 6c) or were unchanged (Fig. 6d) on storage. However, for dispersions stored at 35 and 45°C the dissolution decreased considerably, with the most dramatic decrease observed for the dispersions stored at 45°C.

The ratio between phases was fairly constant during the storage period for all dispersions (Table 4), indicating that the griseofulvin phase was unchanged. This is in agreement with the results from the particle size measurements (Table 5). There are some fluctuations in the mean particle size, but the figures were similar within the standard deviation.

For dispersions prepared with slow cooling (Fig. 7c) the heat of fusion values were slightly increased when stored at 25°C, but more or less unchanged when stored at 35°C. However, for samples stored at 45°C the heat of fusion values decreased with time. This was unexpected as a lower heat of fusion value would lead to an increased dissolution rate. Inspection of the DSC scans (Fig. 5) shows that for dispersions without SDS stored at 45°C for 10 months, the melting started at approx. 80°C, whereas in corresponding dispersions incorporating SDS melting started at approx. 45°C. This will give the lower heat of

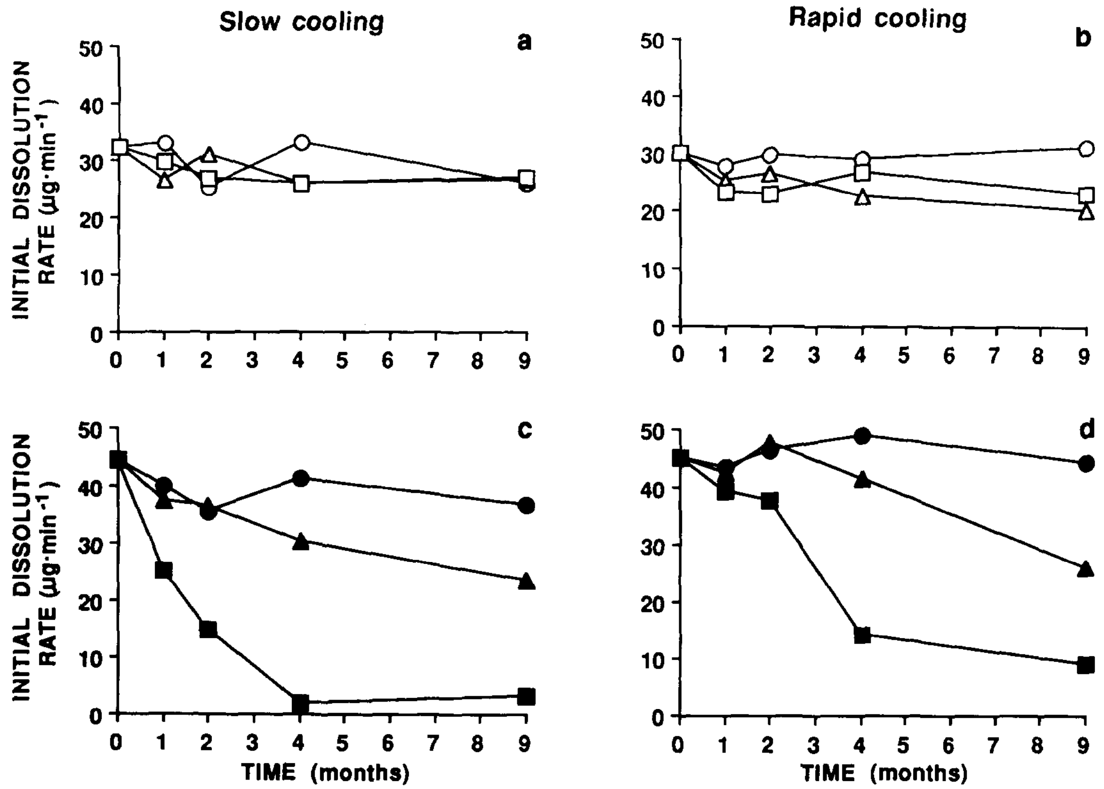

Fig. 6. Initial dissolution rate for solid dispersions of 10% w/w griseofulvin with xylitol as carrier vs storage time: Storage temperature: (○, ●) 25°C; (△, ▲) 35°C; (□, ■) 45°C. Open symbols: no SDS incorporated; Closed symbols: 2% w/w SDS incorporated.

fusion value of the latter as integration was made in the range 70–200°C.

Compacts of freshly prepared dispersions and dispersions stored at 25 and 45°C for 17 months with 10% w/w griseofulvin, with or without 2% w/w SDS, were prepared. During the preparation it was observed that the particles of the dispersion incorporating 2% w/w SDS and stored at 45°C were somewhat sintered and the sample adhered to the punches. For all other samples there were no problems associated with the preparation of compacts.

To give an approximate measure of the dissolution rate of the carrier systems the compacts were tested in a tablet disintegration test apparatus and the time for complete dissolution was registered (Table 6). The compacts eroded in the dissolution medium. For the dispersions without SDS incorporated the carrier dissolution time was approx. 7 min for the freshly prepared dispersion and the dispersions stored at 25 and 45°C. For dispersions incorporating 2% w/w SDS a decrease in dissolution time to approx. 6 min was observed for the freshly prepared dispersion and the dispersion stored at 25°C, which was expected since SDS increases the wettability. However, the dissolution time for the corresponding dispersion stored at 45°C was increased to 11 min. This indicates that the dissolution of xylitol was impaired in dispersions incorporating SDS stored at 45°C.

For dispersions prepared with rapid cooling, the heat of fusion values decreased during storage, the effect being more pronounced with increase in storage temperature. As it had been observed that SDS impaired the dissolution of xylitol when stored at higher temperature for dispersions prepared with slow cooling, it was

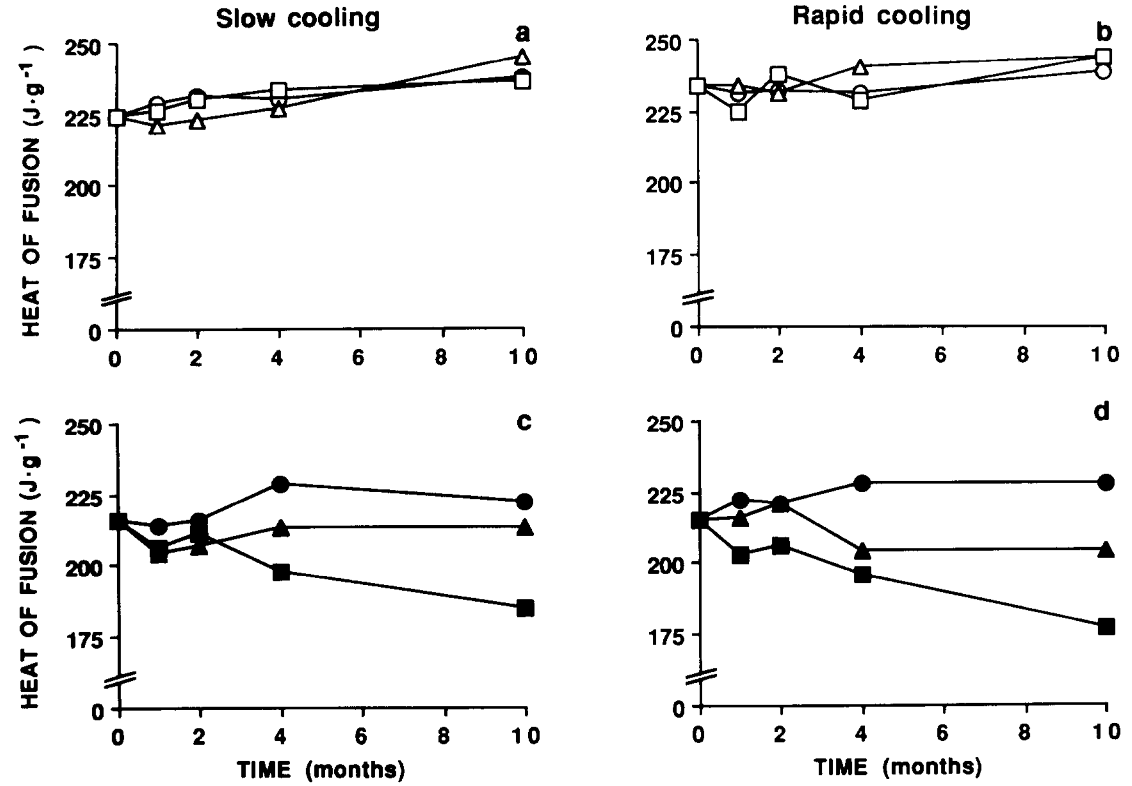

Fig. 7. Heat of fusion of solid dispersions of 10% w/w griseofulvin with xylitol as carrier. Symbols as in Fig. 6.

TABLE 6

Characterization of carrier dissolution from disintegration measurements of compacts [a] of dispersions with 10% w / w griseofulvin in xylitol prepared with slow cooling

Sample (−)	Tablet weight (mg)	Tablet thickness (mm)	Carrier dissolution time [b] (min)
Without SDS			
Freshly prepared	500	3.81	7.0 (0.0)
Stored at 25°C	499	3.87	6.5 (0.3)
Stored at 45°C	500	3.87	7.9 (0.2)
With 2% w/w SDS incorporated			
Freshly prepared	502	3.74	5.7 (0.2)
Stored at 25°C	498	3.79	5.7 (0.1)
Stored at 45°C	495	3.71	11.3 (0.2)

[a] Maximum upper punch pressure constant at 150 MPa.
[b] Mean (S.D.).

assumed that this was also valid for dispersions prepared with rapid cooling.

For dispersions stored at 25 and 35°C the heat of fusion for the second peak was approx. 6–8 J/g. During storage at 45°C the peak decreased, the melting started at a lower temperature dependent on time of storage and the heat of fusion decreased to approx. 3–6 J/g.

It can be concluded that dispersions incorporating SDS stored at 25°C are fairly stable regarding dissolution rate and incorporated state of the drug. With an increase in storage temperature the dissolution rate decreases considerably. This is due to decreased dissolution of xylitol on the incorporation of SDS.

Conclusions

Griseofulvin was present in crystalline form in dispersions with PEG as carrier. In dispersions cooled slowly the dissolution and incorporated state of the drug was unchanged on storage irrespective of storage temperature, whereas in corresponding dispersions prepared with rapid cooling the dissolution rate decreased.

In dispersions incorporating SDS prepared with slow cooling, griseofulvin was dissolved in the PEG/SDS system and the dissolution rate was initially increased considerably. With storage at 25 and 35°C the dissolution decreased, because of precipitation of griseofulvin particles and an impaired dissolution of PEG with the incorporation of SDS. The incorporation of SDS decreased the melting point of PEG and dispersions stored at 45°C were liquified upon storage and were excluded from the study. In corresponding dispersions prepared with rapid cooling, griseofulvin was present in crystalline form. This may have been because the temperature interval at which the monomers of SDS form the aggregates, to which griseofulvin molecules are bound, was passed too quickly. If the aggregates are not formed and the solubility of griseofulvin in the carrier is very low, griseofulvin precipitates as a pure crystalline phase. For these dispersions stored at 25°C the dissolution was unchanged on storage.

In dispersions with xylitol as carrier, griseofulvin was present in crystalline form and the particle size was more or less unchanged on storage irrespective of storage temperature. For dispersions without SDS the dissolution rate was unchanged during the storage period for dispersions prepared with the two cooling procedures. With the incorporation of SDS the dissolution rate increased, but not to the same extent as in dispersions with PEG as carrier. The dissolution rate of dispersions stored at 25°C was unchanged on storage, but with an increase in storage temperature the dissolution decreased considerably. This was due to impaired dissolution of xylitol on the incorporation of SDS.

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